Catecholamine Function in Posttraumatic Stress Disorder: Emerging Concepts

Edited by
M. Michele Murburg, M.D.

Afterword

Matthew J. Friedman, M.D., Ph.D.

The publication of this book is a strong indication that neuro-biological research on PTSD has progressed beyond its descriptive show-and-tell infancy to an adolescence marked by elegant brain research, debates over the appropriateness of different animal models, and hypothesis-driven clinical studies. During the past 10 years it has been established, beyond doubt, that PTSD is associated with psychophysiological and neurobiological abnormalities. Such findings, along with rediscovery of Abram Kardiner's prescient and seminal work (Kardiner 1941; Kardiner and Spiegel 1947), have generated provocative empirical results and theoretical models. The accumulating evidence suggests that PTSD is an extremely complex disorder marked by dysregulation in a number of fundamental neurobiological systems necessary for survival during conditions of extreme stress. Such neurobiological systems are involved in learning, memory, coping, and adaptation. It remains to be shown whether central nervous system (CNS) functions that respond to the normal vicissitudes of life are homologous to or distinctly different from those neurobiological operations set in motion by traumatic stress.

Dr. Michele Murburg has attempted to restrict our focus to one of the major systems through which the pathophysiology of PTSD is expressed. She has shown us the many layers of inquiry needed to explicate catecholaminergic brain mechanisms affected by traumatic stress. In that regard, the book is a comprehensive compilation that achieves a good balance between animal and clinical research as well as between methodological and theoretical issues. Given the depth, breadth, and complexity of information presented in this book, I will attempt to synthesize this material by reviewing it in the context of 12 questions addressed by the authors from their various perspectives.

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What Have We Learned About How Adrenergic Mechanisms Are Altered by Exposure to Trauma?

The locus coeruleus (LC) not only exhibits a basal level of tonic activity but is influenced prominently by a variety of phasic inputs (Aston-Jones et al., Chapter 2; Simson and Weiss, Chapter 3). One of the major inputs to the LC is the nucleus paragigantocellularis (PGi), which is the hub of a network that can simultaneously process information to the LC and peripheral sympathetic nervous system (SNS). It is of great interest that a major source of input to the PGi is the central nucleus of the amygdala, which is involved in conditioned emotional responses and in fear-potentiated startle. Simson and Weiss (Chapter 2) emphasize also that the LC responds to phasic rather than tonic input. Under conditions of inescapable stress the authors demonstrate increased LC activation, which they attribute to a "functional blockade" of $alpha_2$ autoreceptors resulting from depletion (or decreased availability) of norepinephrine. Although such a "blockade" might account for the initial disinhibition of the LC, such a mechanism probably could not be sustained over time under conditions of chronic stress. Instead, one would predict that alpha blockade–induced LC disinhibition should result in downregulation of $alpha_2$ receptors (as discussed by Perry and Lerer et al. in Chapters 12 and 13, respectively).

Charney et al. (Chapter 6) make the link from animal to clinical research, reviewing psychophysiological findings on SNS activation, elevated urinary catecholamine levels, and, most intriguingly, yohimbine-enhanced responses in PTSD patients. Lerer et al. (Chapter 13) and Perry (Chapter 12) report on downregulation of (lymphocyte) beta- and (platelet) $alpha_2$-adrenergic receptors in traumatized war veterans and children. Yehuda and co-workers (Chapter 10) demonstrate elevated urinary catecholamines in war veterans and Holocaust survivors with PTSD. Rausch et al (Chapter 14) show excessive startle response among war veterans with PTSD. Murburg, McFall, and associates (Chapters 8 and 9) report on an increased phasic sympathoadrenal response among war veterans with PTSD to trauma-related stimuli but no alterations in basal SNS tone. Hamner et al. also found no alterations in basal or postexercise stress plasma norepinephrine levels be

tween PTSD patients and control subjects. Their finding that 3-methoxy-4-hydroxyphenylglycol (MHPG) levels are markedly elevated among PTSD patients, compared with control subjects, following exercise suggests increased sensitivity to norepinephrine activation among PTSD patients.

What Other Systems Are Probably Affected and Need to Be Studied (and Have Books Devoted to Them)?

Several chapters address dopaminergic mechanisms. Zacharko's finding (see Chapter 5) that chronic stress exposure reduces the rewarding value of mesocorticolimbic electrical self-stimulation may have clinical relevance to the high prevalence of depressive symptoms among patients with PTSD. Zacharko's work is also of great interest because it demonstrates the importance of 1) the monitoring of such changes longitudinally, 2) an animal's preexposure stress history, and 3) genetic factors (strain differences) that may produce different responses to inescapable shock. Charney et al. (Chapter 6) review animal research on dopaminergic mechanisms and link such findings to PTSD hypervigilance symptoms. Yehuda et al. (Chapter 10) show that urinary dopamine levels are elevated, along with norepinephrine levels, among war veterans and Holocaust survivors with PTSD compared with control subjects.

The review by Charney et al. indicates that inescapable stress also induces alteration in opioid, benzodiazepine, and hypothalamic-pituitary-adrenocortical (HPA) mechanisms. Corticotropin-releasing factor (CRF), benzodiazepines, and opioids influence the PGi-LC system (Aston-Jones et al., Chapter 2), and opioids also significantly affect the dopaminergic mesocorticolimbic reward system (Zacharko, Chapter 5). Two potentially important systems mentioned in passing but never addressed in this book are the serotonergic system, which is targeted by some very promising drugs such as fluoxetine, and the NMDA system, which is implicated in learning, extinction, and memory and may also mediate sensitization following traumatic exposure. Dr. Murburg's book certainly whets our appetite for other books that will focus on any of these important nonadrenergic systems.

Are the Abnormalities in PTSD Tonic or Phasic Alterations in Catecholamine Function?

Evidence presented by several authors indicates that adrenergic abnormalities are phasic rather than tonic. The LC itself is much more responsive to phasic input (Aston-Jones et al., Chapter 2; Simson and Weiss, Chapter 3). Careful clinical studies on the cardiovascular system indicate that phasic, but not basal, pulse rate, blood pressure, and plasma catecholamine levels differentiate PTSD patients from control subjects (Murburg et al., Chapter 9; Hamner et al., Chapter 11; Perry, Chapter 12). This is an important finding that might appear contrary to reports of elevated 24-hour urinary catecholamine levels described in this book (Yehuda et al., Chapter 10) and elsewhere (Kosten et al. 1987). It also might appear contrary to the elevated basal levels of cardiovascular tone reported by many authors, as reviewed by Blanchard (1990) and as reported by Perry in Chapter 12 regarding basal heart rate of children with PTSD. As noted by Murburg et al., however, 24-hour urinary results simply reflect net SNS activity over time and cannot distinguish tonic from phasic changes. These authors argue further that plasma and urinary measurements of catecholamines represent different physiological processes. Veith and Murburg suggest that conflicting results regarding cardiovascular indices may result primarily from methodological differences between investigations.

I believe that given the nature of PTSD we must question the definitions of tonic versus phasic in that context. If, in the course of a day, a PTSD patient is frequently experiencing phasic responses (in the form of waking recollections, nocturnal traumatic nightmares, exposure to trauma-mimetic stimuli, and stimulus generalization/sensitization to more ordinary stressful events), such an accumulation of diurnal phasic catecholamine activity will appear to represent a tonic abnormality under certain experimental conditions and a phasic one under others.

What Is the Nature of the Physiological and Neurobiological Equilibrium That Is Present in PTSD?

Bruce McEwen (personal communication, 1992) has observed that when a playground seesaw is perfectly balanced by two

40-pound children, it is in equilibrium. When the seesaw is perfectly balanced by two 4,000-pound elephants, it is also in equilibrium. The first example represents a *homeostatic* equilibrium, because it is well within the normal response capacity of the system. The second example, according to McEwen, is an *allostatic* equilibrium that exerts tremendous pressure on the system, which may require abnormal compensatory mechanisms that the system may not be able to sustain indefinitely. There is evidence that basal catecholamine function in chronic PTSD is an allostatic rather than a homeostatic equilibrium. The excessive phasic responsiveness reported in several chapters is reminiscent of the latent rebound hyperexcitability present in drug-addicted individuals that is unmasked during acute withdrawal of drugs. Furthermore, evidence from several authors suggests that PTSD patients pay a neurobiological price to achieve a baseline equilibrium that would meet McEwen's definition of allostasis. Simson and Weiss (Chapter 3) report that inescapable stress produces excessive LC excitability, which they attribute to functional blockade of alpha$_2$ receptors. Zacharko (Chapter 5) reports that the mesocorticolimbic reward system is less efficacious following inescapable stress. Clinical studies show lower resting MHPG levels (Hamner et al., Chapter 11), higher urinary norepinephrine and dopamine levels (Yehuda et al., Chapter 10), and down-regulation of platelet alpha$_2$- and lymphocyte beta-adrenergic receptors (Perry, Chapter 12; Lerer et al., Chapter 13). Whether or not tonic physiological or neurobiological alterations actually occur in PTSD patients, it is the allostatic baseline state that serves as substrate for the phasic abnormalities discussed previously. One might even carry these speculations one step further and hypothesize that recovery in PTSD represents a more favorable allostatic equilibrium rather than a return to normal homeostasis. This speculation is based on Yehuda et al.'s data (Chapter 10) showing that Holocaust survivors without PTSD show a (nonsignificant) trend toward lower urinary norepinephrine and dopamine levels than do age- and sex-matched controls. This finding is also consistent zwith Lavie and Kaminer's (1989) report that well-functioning Holocaust survivors without PTSD show less dream recall than do normal control subjects (who, in turn, show less recall than do Holocaust survivors with PTSD).

What Are Current Candidate Animal Models and How Well Do They Fit Research Findings and Clinical Phenomenology?

Since publication of van der Kolk et al.'s (1985) inescapable stress (IES) hypothesis of PTSD, it has been the most frequently cited animal model of this disorder. Indeed, the data reported by Simson and Weiss (Chapter 3) and by Zacharko (Chapter 5) were generated from animals subjected to an IES experimental paradigm. Charney et al. (Chapter 6) show us that there are other candidate animal models that may be as appropriate as, or more appropriate than, IES, including fear conditioning, failure of extinction, and behavioral sensitization/stress sensitivity. Antelman and Yehuda (Chapter 4) offer a delayed sensitization (i.e., time-dependent change [TDC]) model that has a distinct advantage over IES with regard to its capacity to explain the persistence of PTSD symptoms, delayed-onset PTSD, the worsening of untreated PTSD over time, and the development of PTSD after exposure to a single brief traumatic event. Yehuda and Antelman (Chapter 16) courageously take the next step and begin to set down guidelines for animal models of PTSD by identifying those factors that are essential for the induction of PTSD and those that can influence the manifestation or course of the disorder.

In my opinion, because many different traumatic events can lead to PTSD (as many different etiological factors can lead to fever or edema), there may not be a single best model for PTSD. Whereas a sensitization model may be best for PTSD following a single brief exposure such as an automobile accident or certain natural disasters, IES may be better suited for protracted stress such as that produced by war, incest, or torture. TDC and IES are not mutually exclusive and may both be operative under certain circumstances. I believe that any adequate animal model will incorporate the following points: 1) that traumatic exposure is a necessary, not a sufficient, condition for development of PTSD, because all exposed organisms do not develop the disorder; 2) that recovery (or at least attenuation of symptoms) does occur frequently following clinical expression of the full PTSD syndrome (e.g., lifetime prevalence rates are at least twice as great as current prevalence rates); and 3) that the acute response to

trauma may differ among organisms who recover in contrast to those who develop chronic PTSD following traumatic exposure.

Are There Important Methodological Issues That May Explain Conflicting Results?

I have covered much of this ground already with regard to the question of tonic versus phasic changes. Veith and Murburg (Chapter 16) provide an excellent methodological discussion of the many measurement problems that must be solved when monitoring cardiovascular physiology or plasma catecholamines. Similarly, some of the current controversies regarding urinary cortisol levels among PTSD patients (Mason et al. 1986; Pitman et al. 1991) may have more to do with methods of collection and choice of preservative reagents and biochemical analytic techniques than with observable differences.

What About Control Groups?

Lerer and associates (Chapter 13) provide a very instructive chapter. It seems to make a difference whether PTSD patients are compared with nontraumatized control subjects or with similarly traumatized groups without PTSD. Lerer et al. also mention their unpublished observations that "combat experience per se may influence alpha$_2$-adrenergic receptor function in platelets to an extent that differentiates Vietnam veterans with a combat history (with or without PTSD) from noncombatant individuals." Similarly, Yehuda et al. (Chapter 10) show that Holocaust survivors without PTSD have lower urinary catecholamine levels than control subjects, whereas Holocaust survivors with PTSD have higher levels than control subjects. Finally, McFall and Murburg report that combat-exposed veterans without PTSD had lower resting heart rate and blood pressure than did nonexposed control subjects. Besides the intrinsic interest of these deviations from "normal" found in traumatically exposed non-PTSD cohorts (with regard to questions about adaptation, recovery, and allostasis), such differences may have an important effect on data analysis and its implications.

Because of this problem, clinical studies with PTSD patients

will be more interpretable if they include both nonexposed and non-PTSD traumatically exposed comparison groups.

Is the PTSD Diagnosis Meaningful With Regard to Alterations in Catecholamine Function?

It is now well established that psychometric and psychophysiological assessment of PTSD is both reliable and valid (Keane et al. 1987; Kulka et al. 1990). In this book strong evidence is presented that people who meet PTSD diagnostic criteria will exhibit abnormalities in catecholamine function as indicated by urinary catecholamine levels, SNS reactivity, and SNS baseline indices (Yehuda et al., Chapter 10; Murburg et al., Chapter 9; Hamner et al., Chapter 11; Perry, Chapter 12). Furthermore, it appears that psychometrically measured symptom severity is linearly correlated with the severity of catecholaminergic abnormalities. This is shown most explicitly by Yehuda et al., who found significant correlation between PTSD symptom severity and urinary norepinephrine and dopamine levels. I find the comparison between PTSD inpatients and PTSD outpatients most interesting in this regard, because the inpatients had significantly higher urinary catecholamine levels as well as higher PTSD symptom severity than the outpatients. This is consistent with preliminary (unpublished) results obtained at the National Center for PTSD indicating that among hospitalized Vietnam veterans with PTSD, the magnitude of urinary neurohormone abnormalities correlates with PTSD symptom severity (as measured by a number of psychometric instruments). Such data suggest that altered catecholamine function in PTSD may be useful as a dimensional as well as a categorical index of symptomatology. Finally, based on observations with Holocaust survivors and war veterans, it appears that these catecholaminergic abnormalities persist as long as PTSD symptoms persist.

Does the Nature of the Trauma Seem to Make a Difference?

Data reported in this book were obtained mostly on male war veterans but also on a small number of traumatized children and Holocaust survivors who were both male and female. Some com-

parisons across groups are possible. Both traumatized children and war veterans exhibit downregulation of alpha$_2$ receptors (Lerer et al., Chapter 13; Perry, Chapter 12) as well as augmentation of the acoustic startle reflex (Rausch et al., Chapter 14). Both Holocaust survivors and war veterans exhibit elevated urinary catecholamine levels (Yehuda et al., Chapter 10).

Obviously much more neurobiological research is needed with rape/incest, political torture, natural disaster, and industrial accident survivors with PTSD to determine the generalizability of these findings. Very few neurobiological data have been published to date on women with PTSD. Nor is there much information on racial/genetic factors that might influence the neurobiological expression of PTSD. Because all neurobiological research has been conducted on patients from Western industrialized nations, there is no information on PTSD patients from traditional nonindustrialized societies. This is particularly pertinent to cross-cultural questions concerning the applicability of the PTSD model to traumatized individuals from non-Western ethnocultural backgrounds (Friedman and Jaranson, in press; Marsella et al. 1993). If ethnocultural factors affect the phenomenological expression of posttraumatic symptoms (especially with regard to avoidant/numbing symptoms) in such a way that severely traumatized individuals from certain societies do not meet the DSM-III-R diagnostic criteria (American Psychiatric Association 1987), it may only be through neurobiological assessment that we can rule in or rule out the universality of a posttraumatic stress syndrome.

How Are We to Understand the Relationship Between PTSD and Major Depressive Disorder?

According to Lerer et al. (Chapter 13), 95% of the Israeli combat veterans with PTSD who were studied also met diagnostic criteria for major depressive disorder (MDD). Other studies have also shown high rates of comorbidity between PTSD and MDD in both community and treatment-seeking cohorts (Green et al. 1989; Kulka et al. 1990). Findings regarding HPA function show that PTSD patients have significantly lower 24-hour urinary cortisol levels (Mason et al. 1986) and significantly more lymphocyte

glucocorticoid receptors (Yehuda et al. 1991b) than do MDD patients. Furthermore, whereas MDD patients often show non-suppression of the HPA system following dexamethasone, PTSD patients show supersensitive HPA suppression following doses of dexamethasone that do not affect normal subjects (Yehuda et al. 1991a). These HPA axis abnormalities suggest that when comorbid with PTSD, MDD is a different disorder than MDD presenting like classic melancholia (i.e., MDD without PTSD). Results reported in this book on catecholamine function in PTSD add more weight to this argument. PTSD patients show significantly fewer platelet alpha$_2$ receptors, whereas depressed patients show an equal or greater number of these receptors than do normal control subjects (Perry, Chapter 12; Lerer et al., Chapter 13). Murburg et al. (Chapter 8) monitored SNS function in PTSD patients with and without MDD because the authors expected that increased SNS activity previously reported among MDD patients would distinguish the two groups. However, they found no significant differences between the PTSD alone and the comorbid PTSD/MDD groups, suggesting that increased SNS activity does not occur when MDD is comorbid with PTSD. All of these findings on both HPA and catecholamine function suggest that the DSM-III-R (which relies exclusively on phenomenology) cannot be used to distinguish between true melancholia and a depressive manifestation of PTSD that has a distinctly different pathophysiology. Perhaps a clue to the underlying neurobiological abnormality can be found in Zacharko's results (see Chapter 5) suggesting that IES reduces the rewarding value of intracranial self-stimulation mediated by the mesocorticolimbic system.

What Are the Sequelae of Traumatic Exposure Among Young Children?

Perry (Chapter 12) provides an excellent review of current literature on traumatic exposure and raises two fundamental concerns. First, traumatic exposure before age 3 can produce altered development of the CNS and developmental delay, and can result in stable autonomic hyperarousal. These are important clinical observations that should be systematically investigated, using the animal model paradigms mentioned earlier, with animals at

various stages of development. Second, Perry invokes a diathesis-stress model in which age of traumatization and family psychiatric history are the major predictive factors. (In Chapter 5, Zacharko has demonstrated how strain differences significantly influence an animal's response to an inescapable stress condition.) Perry reports that traumatized children from schizophrenic families are more likely to develop prepsychotic or psychotic symptoms, whereas children with an affective/anxiety family history are more likely to develop mood and anxiety symptoms. Besides the obvious implication of genetic factors, these findings also indicate that traumatic exposure may strongly influence the expression of other major psychiatric disorders besides PTSD.

What Do Those Findings Suggest About Treatment?

Because there have been so few randomized double-blind controlled trials of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), Southwick et al.'s quantitative review of open as well as controlled trials (see Chapter 15) is very helpful. Their conclusion that TCAs and MAOIs seem to have specific efficacy on global and intrusive PTSD symptoms but appear ineffective against avoidant/numbing symptoms is consistent with less quantitative literature reviews (Friedman 1991, in press). Since hyperarousal symptoms were monitored infrequently (because most investigations relied on the Impact of Event Scale), it is too early to reach any conclusions in that regard. Southwick et al.'s analysis suggests that adequate pharmacotherapy for PTSD may necessitate the prescribing of several different classes of drugs to attenuate dysregulation in a number of neurobiological systems affected in PTSD. Indeed, basic research in this book supports this speculation, as opioids, benzodiazepines, and CRF profoundly affect (while serotonin and NMDA agonists may also influence) CNS mechanisms that mediate the organism's response to chronic stress (Aston-Jones et al., Chapter 2; Simson and Weiss, Chapter 3; Zarcharko, Chapter 5; Charney et al., Chapter 6). Finally, Perry demonstrates the efficacy of the alpha$_2$ agonist clonidine on PTSD and other symptoms among children who had been exposed to traumatic stress. Clearly, we have just begun to carefully evaluate different phar-

macotherapeutic approaches to PTSD.

This book, *Catecholamine Function in PTSD: Emerging Concepts,* is a giant step forward. It helps us ask better questions, conceptualize clinical data from a basic neurobiological perspective, and develop animal models that may be more pertinent to PTSD. Dr. Murburg has made a significant contribution by compiling and synthesizing all of this material. She deserves thanks from all of us.

REFERENCES

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised. Washington, DC, American Psychiatric Association, 1987

Blanchard EB: Elevated basal levels of cardiovascular response in Vietnam veterans with PTSD: a health problem in the making? Journal of Anxiety Disorders 4:233–237, 1990

Friedman MJ: Biological approaches to the diagnosis and treatment of post-traumatic stress disorder. Journal of Traumatic Stress 4:67–91, 1991

Friedman MJ: Biological and pharmacological aspects of the treatment of PTSD, in Handbook of Post-Traumatic Therapy. Edited by Williams MB, Sommer JF. Westport, CT, Greenwood Press (in press)

Friedman MJ, Jaranson JM: The applicability of the PTSD concept to refugees, in In Peril and Pain: The Mental Health and Well-Being of the World's Refugees. Edited by Marsella AJ, Borneman TH, Orley J. Washington, DC, American Psychological Press (in press)

Green BL, Lindy JD, Grace MC, et al: Multiple diagnosis in posttraumatic stress disorder: the role of war stressors. J Nerv Ment Dis 177:329–335, 1989

Kardiner A: The Traumatic Neuroses of War (Psychosomatic Medicine, Monograph I-II). Washington, DC, National Research Council, 1941

Kardiner A, Spiegel H: The Traumatic Neuroses of War. New York, Paul Hoeber, 1947

Keane TM, Wolfe J, Taylor KL: Post-traumatic stress disorder: evidence for diagnostic validity and methods of psychological assessment. J Clin Psychol 43:32–43, 1987

Kosten TR, Mason JW, Giller EL, et al: Sustained urinary norepinephrine and epinephrine elevation in post-traumatic stress disorder. Psychoneuroendocrinology 12:13–20, 1987

Kulka RA, Schlenger WE, Fairbank JA, et al: Trauma and the Vietnam War Generation. New York, Brunner/Mazel, 1990

Lavie P, Kaminer H: Holocaust survivors' coping with bereavement as reflected in sleep and dreaming forty years later, in Biological Aspects of Non-psychotic Disorders. Abstract from the scientific proceedings of the World Federation of Biological Psychiatry, Jerusalem, 1989, No 147

Marsella AJ, Friedman MJ, Spain EH: Ethnocultural aspects of PTSD, in American Psychiatric Press Annual Review of Psychiatry, Vol 12. Edited by Oldham JM, Riba MB, Tasman A. Washington, DC, American Psychiatric Press, 1993, pp 157–181

Mason JW, Giller EL Jr, Kosten TR, et al: Urinary free-cortisol in post-traumatic stress disorder. J Nerv Ment Dis 174:145–149, 1986

Pitman RK, Orr SP, Meyerhoff JL, et al: Urinary cortisol excretion in PTSD. Paper presented at the 144th annual meeting of the American Psychiatric Association, New Orleans, LA, May 1991

van der Kolk BA, Greenberg M, Boyd H, et al: Inescapable shock, neurotransmitters, and addiction to trauma: toward a psychobiology of post-traumatic stress. Biol Psychiatry 20:314–325, 1985

Yehuda R, Giller EL Jr, Boisoneau D, et al: The low-dose DST in PTSD, in 1991 New Research Program and Abstracts, 144th annual meeting of the American Psychiatric Association, New Orleans, LA, May 1991a, NR324, pp 125–126

Yehuda R, Lowy MT, Southwick SM, et al: Lymphocyte glucocorticoid receptor number in posttraumatic stress disorder. Am J Psychiatry 148:499–504, 1991b